07-19-06

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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:

Pau et al.

Serial No.: 09/722,867

Filed: November 27, 2000

For: PRODUCTION OF VACCINES

Confirmation No.: 4248

Examiner: M. Hill

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BRIEF ON APPEAL

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Sirs:

This brief is submitted as a single copy pursuant to 37 C.F.R. § 41.37 and in the format required by 37 C.F.R. § 41.37(c) (1):

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(1) REAL PARTY IN INTEREST

The real party in interest in the present pending appeal is Crucell Holland B.V., assignee of the pending application as recorded with the United States Patent and Trademark Office on November 3, 2003, at Reel 014649, Frame 0758.

(2) RELATED APPEALS AND INTERFERENCES

Neither the appellants, the appellants' representative, nor the assignee are aware of any pending appeal or interference which would directly affect, be directly affected by, or have any bearing on the Board's decision in the present pending appeal.

(3) STATUS OF CLAIMS

Claims 1 through 35, 37, 41, and 46-49 were cancelled without prejudice or disclaimer.

Claims 36, 38, 39, 45, and 52 were withdrawn from consideration.

Claims 40, 42 through 44, 50, and 51 stand rejected.

No claims are allowed.

The rejections of claims 40, 42 through 44, 50, and 51 are being appealed.

(4) STATUS OF AMENDMENTS

The appellants' amendments, filed November 28, 2005, have been entered.

(5) SUMMARY OF CLAIMED SUBJECT MATTER

The claimed invention provides methods for concentrating influenza virus. The invention provides a method for concentrating influenza virus from a cell-cleared supernatant comprising the process of ultrafiltrating the supernatant using a hollow fiber under low shear conditions. *See*, Specification at ¶¶ 83-86, 117, and 121. In one aspect, the invention provides that the cell cleared supernatant be obtained from *in vitro* cultured cells. *Id.* at ¶¶ 86, 117-121, and claim 42. In another aspect, the ultrafiltration is performed using a filter comprising a cut-off of 750 KD. *Id.* at ¶¶ 86, 121 and claims 43 and 51. In a further aspect, the concentration of the influenza virus comprises at least a partial removal of proteins comprising a molecular weight smaller than 750 KD. *Id.* at ¶ 86 and claims 44, 50, and 51.

(6) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

A.Whether claims 40, 42-44, 50, and 51 are unpatentable under 35 U.S.C. § 103(a) over Merten *et al.* (Production of influenza virus in cell cultures for vaccine preparation, *Exp. Med. Biol.* 1996 B., 397:141-51) (hereinafter "Merten") in view of Paul *et al.* (Increased viral titer through concentration of viral harvests from retroviral packaging lines, *Hum. Gene Ther.* 1993 Oct;4(5):609-15) (hereinafter "Paul").

(7) ARGUMENT

(i) 35 U.S.C. § 103(a)

Claims 40, 42-44, 50, and 51 stand rejected under 35 U.S.C. § 103(a) as assertedly being obvious over Merten in view of Paul.

Independent claim 40 recites "a method for concentrating an influenza virus that is or can be made infectious, said method comprising: obtaining a cell-cleared supernatant comprising said influenza virus from a culture of cells; and ulrafiltrating said supernatant under low shear conditions using a hollow fiber; and concentrating the virus."

Dependent claim 42, recites "the method according to claim 40, wherein said culture of cells comprises an *in vitro* cultured cells."

Dependent claim 43 recites "the method according to claim 40, wherein said ultrafiltrating is performed with a filter comprising a cut-off of 750 KD.

Claims 44, 50, and 51 depend from claims 40, 42 and 43 respectively. Each of claims 44, 50, and 51 recites, with respect to its base claim, "wherein said concentrating further comprises at least a partial removal of proteins comprising a molecular weight smaller than 750 KD."

Alleged Basis of the Rejections

As to claims 40, 42-44, 50, and 51, the Examiner, in the Office Action mailed July 27, 2005 at Page 3, alleges that "Merten teaches that the crude cell culture supernatant containing

influenza virus from *in vitro* cultured cells from a bioreactor is clarified first and that the virus is ultra-centrifuged through a gradient (filtering by density) under low shear conditions (page 143, last paragraph)." Further, the Examiner admits that "while Merten does not state 'low shear' conditions, the step of gradient purification is known to preserve infectivity and thus keep the virus intact, not shearing it." *Id.* In regards to elements missing from the teachings of Merten, the Examiner admits that "Merten does not teach hollow fiber centrifugation." *Id.* at page 4.

With regard to the teachings of Paul, the Examiner asserts that:

> Paul teaches ultracentrifugation of viruses with hollow fibers with a 500,000 MW cut off (500kDa.) and this results in a 10-30X concentration (page 610, column 1, lower paragraph). Paul also teaches that the infectivity of the input virus in maintained (page 610, top).
>
> One of ordinary skill in the art at the time of the invention would have been familiar with the handling of influenza for different uses. One of ordinary skill in the art would have been motivated to clarify and use a hollow fiber ultracentrifugation to concentrate the virus because gradient ultracentrifugation which is a procedure that requires time, expensive materials, and expensive equipment. The use of filters with cut-off values is known in the art of handling cell culture supernatants and the choice of a specific cut-off would be determined.
>
> Thus, it would have been *prima facie* obvious to concentrate the virus of Merten using hollow fiber ultracentrifugation with the expectation of success in increasing the concentration of influenza virus and purifying it. *Id.* at pages 4-5.

In the Office Action mailed February 22, 2006 at Page 4, the Examiner further asserts that

> While Paul shows initial low infection recovery on page 610, further experiments show higher levels of recovery. It is routine to optimize parameters as shown by Paul and routine optimization is not undue burden.

No Motivation To Combine

With respect to each of the claims at issue in this appeal, there is no motivation to combine the references of Merten and Paul. The Examiner alleges that "one of ordinary skill in the art would have been motivated to clarify a supernatant and use a hollow fiber ultracentrifugation to concentrate the virus because gradient ultracentrifugation is a procedure that requires time, expensive materials, and expensive equipment." Office Action mailed July

27, 2005, pages 4-5. Appellants respectfully assert that the Examiner's provided motivation is improper and believe that no motivation to combine the references exists.

"[The] factual question of motivation is material to patentability and [cannot] be resolved on subjective belief and unknown authority." *In re Lee*, 61, U.S.P.Q.2d, 1430, 1434 (Fed. Cir. 2002). "[T]he Board must not only assure that the requisite findings are made, based on evidence of record, but must also explain the reasoning by which the findings are deemed to support the agency's conclusion." *Id.* In the present case, the Examiner relies on an assertion that there is motivation to combine the references "because gradient ultracentrifugation is a procedure that requires time, expensive materials, and expensive equipment." However, the Examiner has provided no evidence of the time, expense, or equipment involved in gradient ultracentrifugation or in hollow fiber ultrafiltration. The Examiner seems to assert that the time, expense, and equipment involved for hollow fiber ultrafiltration would be decreased relative to that for ultra-centirfugation. However, the time required for hollow fiber centrifugation is substantial (2-6 hours) (Paul at page 610) and the hollow fiber methods require specialized filters and equipment including devices to regulate a constant pressure against the filter over the course of the purification (*Id.*). As such, appellants submit that the Examiner has not provided any reasoning or evidence to support his assertion that gradient ultracentrifugation is a more expensive procedure in terms of time, materials, and equipment. As such, in view of the ruling made in *In re Lee*, appellants submit that the Examiner has not provided a proper motivation to combine the references.

The Examiner further asserts that the hollow fiber ultrafiltration methods taught in Paul are generally applicable. However, where Paul discusses the general applicability of the methods taught, the general applicability is related specifically to retrovirus preparation. *See, e.g.,* Paul at page 613, first sentence under "Discussion." As such, the authors of Paul viewed their disclosure as generally relevant to retrovirus preparation, but make no teachings as to the relevance or applicability of the methods to the concentration of other virus types such as influenza virus.

In addition, one would not be motivated to combine Merten with Paul as there are still serious unexplained flaws in the outcome of the process taught by Paul. As can be seen in Table 2 of Paul, certain unexplained changes caused by the isolation regime of Paul radically change

the infectivity of the isolated retroviruses in regard to certain cell types. Specifically, the infection frequency on Jurkat cells is, at best, 37% of what is expected based on the titers determined on NIH-3T3 cells. In the worst example, the infection frequency is only 5% of what is expected. Such results strongly suggest that there is something in the isolation processing that is altering the retrovirus in such a way that it has a much lower infection efficiency on cells it is known to infect. As such, one of skill in the art would not be motivated to use the isolation protocol of Paul as there are serious undefined effects of the process that can drastically alter retrovirus function, with even more uncertain results when applied to influenza production.

For at least the foregoing reasons, appellants respectfully submit that the Examiner has not provided the requisite proper motivation to combine the references, and that one of ordinary skill in the art would not be motivated to combine the references as they teach a process with serious flaws. As such, appellants respectfully request that the rejections of claims 40, 42-44, 50, and 51 under 35 U.S.C. § 103(a) be withdrawn and the claims allowed.

No Reasonable Expectation of Success

The Examiner alleges that it would have been "obvious to concentrate the virus of Merten *et al.* using hollow fiber filtration with the expectation of success in increasing the concentration of influenza virus and purifying it." (Office Action, mailed July 27, 2005, at page 5). However, with respect to all of the claims at issue in this appeal, appellants assert that no reasonable expectation of success exists in using the retroviral techniques of Paul in the very different field of vaccine production for influenza virus. No indication is present in the cited references that the hollow fiber method as provided by Paul would also be applicable to the disclosure of Merten or that the skilled person would be motivated by the teachings of the cited references to use hollow fiber filtration to purify an influenza virus.

Appellants submit that Paul does not enable the concentration of influenza viruses using the described hollow fiber method, wherein such viruses remain infectious or can be made infectious. It would only be after burdensome experimentation and investigation that one of skill in the art could decide the utility of hollow fiber filtration for concentrating an influenza virus. Moreover, Paul admits that the success of isolating infectious retroviral particles depended on using specific filtration parameters and, even using those parameters, the retroviral infectivity

was sometimes very low, presumably because of high shear forces (Paul at page 610). Further, the isolated retrovirus was inexplicably deficient at infecting certain cell types (*Id.* at Table 2). Accordingly, one of skill in the art would not have a reasonable expectation of success for concentrating influenza viruses that are infective or can be made infective under low shear conditions in view of the teachings of Paul with respect to retroviruses.

Appellants assert that, even though hollow fiber filtration was known at the time of the application, those of skill in the art knew that different filtration techniques were more appropriate depending on the type of viral isolates. The cited references make no indication that an influenza virus could be concentrated using a hollow fiber filter system or that one would obtain infectious influenza virus after using a hollow fiber filter. Retroviruses (as purified in Paul) may very well behave completely different than other viruses such as influenza virus. As there is no indication in the cited references that the hollow fiber method would work for influenza, appellants submit there would have been a need for an inventive step to provide a method as claimed in the present application.

Accordingly, a *prima facie* case of obviousness cannot be established because the cited references do not alone, or in combination, provide a reasonable expectation of success. Therefore, appellants the rejections of claims 40, 42-44, 50, and 51 under 35 U.S.C. § 103(a) be withdrawn and the claims allowed.

References Do Not Teach Each And Every Element Of Claims 43 And 51

To establish a *prima facie* case of obviousness the prior art reference (or references when combined) must teach or suggest all the claim elements. *In re Vaeck*, 0947 F.2d 488 (Fed. Cir. 1991). Appellants assert, that as to claims 43 and 51, the references fail to teach or suggest each and every element of the claims.

Claim 43 recites "the method according to claim 40, wherein said ultrafiltrating is performed with a filter comprising a cut-off of 750 KD." Appellants assert that the references, when combined, do not teach or suggest the use of a filter having a cut-off of 750 KD for the use of concentrating an influenza virus. As asserted by the Examiner, Merten does not teach hollow fiber ultracentrifugation and Paul teaches the ultracentrifugation of retroviruses with a 500,000 MW cut-off (500 kDa). Office Action mailed July 27, 2005, at page 4. The Examiner further

asserts that the use of filters with cut-off values is known in the art of handling cell culture supernatants and the choice of a specific cut-off would be determined. *Id.* at page 5.

As admitted by the Examiner, the references do not teach or suggest the use of a filter having a cut-off of 750 KD. In an attempt to remedy this lack of teaching or suggestion, the Examiner appears to take official notice that one of ordinary skill in the art would choose a filter with a cut-off of 750KD for the concentration of influenza viruses based on the common knowledge of one of ordinary skill in the art. However, it is never appropriate to rely solely on "common knowledge" in the art without evidentiary support in the record. *In re Zurko*, 258 F.3d 1379, 1385 (CCPA 1979) ("[T]he Board cannot simply reach conclusions based on its own understanding or experiences, - or on its assessment of what would be basic knowledge or common sense. Rather the Board must point to some concrete evidence in the record in support of the findings"). "If the Examiner is relying on personal knowledge to support the fining of what is known in the art, the Examiner must provide an affidavit or declaration setting forth specific factual statements and explanation to support the finding." MPEP 2144.04, citing 37 CFR 1.104(d)(2). If the Examiner is taking official notice of facts not in the record, then "the basis for such reasoning must be set forth explicitly" and the Examiner "must provide specific factual findings predicated on sound technical and scientific reasoning to support his or her conclusion of common knowledge." MPEP 2144.03. Appellants submit that the Examiner has provided no evidentiary support on the record that one of ordinary skill in the art would use a filter comprising a cut-off of 750 KD for the purification of influenza virus and that the Examiner has thus failed to show that "the choice of a specific cut-off would be determined" as being 750 KD.

In light of the foregoing remarks, appellants respectfully assert that the Merten and Paul when combined do not teach the use of a filter comprising a cut-off of 750 KD. Appellants further assert that the Examiners unsupported statement regarding the determination of a specific cut-off is without evidentiary support in the record and cannot properly form the basis of a rejection under 35 U.S.C. § 103(a). As such, appellants respectfully request that the rejection of claim 43 under 35 U.S.C. § 103(a) be withdrawn and the claim allowed.

Further as claim 51 depends from claim 43, appellants assert that claim 51 is at least allowable as depending from a non-obvious base claim. As such, appellants respectfully request that the rejection of claim 51 under 35 U.S.C. § 103(a) be withdrawn and the claim allowed.

(8) CLAIMS APPENDIX

40. A method for concentrating an influenza virus that is or can be made infectious, said method comprising:

obtaining a cell-cleared supernatant comprising said influenza virus from a culture of cells;

ultrafiltrating said supernatant under low shear conditions using a hollow fiber; and

concentrating the virus.

42. The method according to claim 40, wherein said culture of cells comprises *in vitro* cultured cells.

43. The method according to claim 40, wherein said ultrafiltrating is performed with a filter comprising a cut-off of 750 KD.

44. The method according to claim 40, wherein said concentrating further comprises at least a partial removal of proteins comprising a molecular weight smaller than 750 KD.

50. The method according to claim 42, wherein said concentrating further comprises at least a partial removal of proteins comprising a molecular weight smaller than 750 KD.

51. The method according to claim 43, wherein said concentrating further comprises at least a partial removal of proteins comprising a molecular weight smaller than 750 KD.

(9) EVIDENCE APPENDIX

NONE.

(10) RELATED PROCEEDINGS APPENDIX

NONE.

Respectfully submitted,

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